UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/788,110	02/15/2001	Maurizio Zanetti	UCSD-07017	2849

23535 7590 07/02/2007

MEDLEN & CARROLL, LLP
101 HOWARD STREET
SUITE 350
SAN FRANCISCO, CA 94105

EXAMINER	
UNGAR, SUSAN NMN	
ART UNIT	**PAPER NUMBER**
1642	

MAIL DATE	DELIVERY MODE
07/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/788,110	ZANETTI, MAURIZIO	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *05 April 2007*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *42-51* is/are pending in the application.

4a) Of the above claim(s) *48 and 51* is/are withdrawn from consideration.

5)☐ Claim(s) *43 and 44* is/are allowed.

6)☐ Claim(s) *42, 45-47, 49-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. The Amendment filed April 5, 2007 in response to the Office Action of October 3, 2006 is acknowledged and has been entered. Previously pending claims 1-41 have been cancelled and new claims 42-51 have been added. Claims 48 and 51 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 42-47, 49-50 are currently being examined.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 42, 45-47, 49-50 are rejected under 35 USC 112, first paragraph because while enabling for an isolated peptide consisting of the amino acid of SEQ ID NO:1 or SEQID NO:2 does not reasonably provide enablement for an isolated peptide consisting of the amino acid sequence of SEQID NO:21 or SEQ ID NO:22. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

The claims are drawn to a peptide consisting of SEQ ID NO:21 and SEQ ID NO:22 wherein, for the reasons set forth below, neither of these peptides has been demonstrated to be a naturally processed hTRT peptide.

The specification teaches at paragraph 0024 of the published application that telomerase is an enzyme that tumor cells produce and require to remain

alive, but which normal body cells (except for sperm and hematopoietic system) neither produce nor require. This unique property of telomerase has prompted attempts to develop a drug that will block the action of the enzyme sufficiently to either inhibit the growth of new tumor cells or cause the death of older ones. Telomerase is an example of a class of substances that are often referred to as being "tumor-specific" because they are needed and/or used by tumor cells in differentially larger amounts than by normal healthy cells of the body. The specification further teaches that the invention is drawn to a vaccine that is universally effective against any proliferating tumor (para bridging pages 6-7), wherein the invention is specifically drawn to a vaccine comprising an hTRT peptide that is effective for initiating and enhancing a CTL response against mammalian cancer cells (p. 7, lines 1-5). The specification hypothesizes that the generation of endogenously-processed telomerase peptides bound to Class I MHC molecules could target CTL to tumors of different origins. The specification further hypothesizes that this could advance vaccine therapy against cancer provided that precursor CTL recognizing telomerase peptides in cancer patients can be expanded through immunization. The specification demonstrates that the majority of patients with prostate Ca immunized *in vitro* against SEQ ID Nos: 1 and 2 develop hTRT specific CTL, wherein it was found that cancer patients' CTL specifically lysed a variety of HLA-A2+ cancer cell lines (p. 10, lines 13-23).

The specification further teaches that at page 12 that hTRT is in all respects a self antigen. Consequently, CD8+ T lymphocytes with a receptor for MHC/hTRT peptide complexes are expected to be eliminated during thymic negative selection, reducing the potential precursor T cell repertoire and

imposing limitations on their expansion upon encounter with tumor cells in adult life. Additionally, stimulation by antigen in the absence of a second signal induces clonal anergy further hampering the potential repertoire. The extent to which these events affect the normal adult repertoire, and whether or not exposure to hTRT during cancer formation has any adverse effect on the ability of cancer patients to respond, is not known. Because answering these questions is relevant to future strategies of immune intervention targeted at hTRT, the ability of cancer patients to mount a CTL response in vitro against SEQ ID NOS 1 and 2 was analyzed.

The specification specifically demonstrates that SEQ ID NOS 1 and 2 represent endogenously-processed hTRT peptides by demonstrating that lysis of LnCap tumor cells by **CTL from a prostate cancer patient** (emphasis added) could be dose-dependently inhibited by SEQ ID NO:1 or 2 peptide-loaded T2 cells (a human T cell leukemia/B cell line) (p. 19, lines 12-20).

In additional assay data, the specification discloses that SEQ ID NO:21 was found to have lower affinity binding than SEQ ID NO:1 and that SEQ ID NO:21 was modified by replacing the "R" residue with a "Y" residue because this modification "is supposed to increase the binding affinity to HLA-A2 and also its immunogenicity (p. 27, lines 19-21) wherein it was found that CTL generated *in vitro* from normal PMBC against the modified SEQ ID NO:22 were able to lyse a melanoma cell line (p. 27, lines 24-27).

One cannot extrapolate the teaching of the specification to the scope of the claims because although the intended use of the peptides for pharmaceutical purposes is no longer recited in the claims and SEQ ID NO:1 and SEQ ID NO:2 are now enabled because of the clear teaching in the

specification that lysis of LnCap cells with CTL from a prostate cancer patient could be inhibited with T2 cells loaded with SEQ ID NO:1 and SEQ ID NO:2, clearly demonstrating that prostate cancer patient presents with CTL against those peptides and that the peptides are naturally processed hTRT peptides which induce CTL in patient, *in vivo* wherein one of ordinary skill in the art would immediately envision the enabled use for those peptides of binding to CTL from prostate cancer patient for diagnosis of disease, the same cannot be said for SEQ ID NOS 21 and 22.

The only teaching in the specification drawn to SEQ ID NOS 21 and 22 is that SEQ ID NO:21 was found to have lower affinity binding than SEQ ID NO:1 and that SEQ ID NO:21 was modified by replacing the "R" residue with a "Y" residue because this modification "is supposed to increase the binding affinity to HLA-A2 and also its immunogenicity (p. 27, lines 19-21) wherein it was found that CTL generated *in vitro* from normal PMBC against both the modified SEQ ID NO:22 and SEQ ID NO:21 were able to lyse a melanoma cell line (p. 27, lines 24-27).

Although Examiner stated previously that SEQ ID NO:22, was enabled in composition, wherein the peptide stimulated CTL for lysis of cancer cells *in vitro* upon recognition of naturally processed hTRT peptides, upon review and reconsideration it is clear that SEQ ID NO:22 is not a naturally processed hTRT peptide since it is a modification of SEQ ID NO:21 and it has become clear that there is no information in the specification that indicates that SEQ ID NO:21 is in fact a naturally processed hTRT peptide *in vivo* in patients with any form of cancer or that it would produce CTL that would recognize primary cancer cells *in vivo*. Given the above, it could not be predicted that the CTL

produced could be used for cancer treatment in passive immunization techniques or that the claimed peptides could stimulate CTL effective for cancer treatment and thus one would not know how to use the CTL produced or the peptides that stimulated that production. Given that the claims are interpreted in light of the specification, it is clear that the only intended use for the claimed peptides is as a universal vaccine for the treatment of cancer/stimulation of CTL effective for the treatment of cancer.

As previously set forth, the unpredictability of the effectiveness of peptides that stimulate CTL that lyse cancer cells are well known in the art. In particular, the art teaches the unpredictability of treating cancer using peptide-based vaccines to elicit a CTL response, particularly regarding self-antigens. Especially relevant is the teaching of Lee et al (J. Immunol., 1999, 163:6292-6300), who specifically teach that although a peptide-based vaccine can effectively generate a quantifiable T cell-specific immune response in the PBMC of cancer patients, this response does not associate with a clinically evident regression of metastatic melanoma (see abstract), thus effective treatment with any peptide, even a peptide that will induce a CTL response in vitro is not predictable.

Further, Kirkin et al, of record teach that in particular for tumor antigens (even with the existence of precursor CTL), due to the existence of self-tolerance, only T cells with low affinity T-cell receptors are produced (abstract). Further, Chaux et al, of record teach some of the CTLs have an affinity that is too low for the recognition of cells that have processed the antigen, which is different from the *in vitro* conditions like those presented in the instant specification, in which the synthetic peptides are in high number

when incubated with the cells (p.541, second column, second paragraph). Given that there is no information in the specification as originally filed that the claimed peptides are naturally processed hTRT peptides *in vivo* in patients, it could not be predicted that the peptides would be recognized *in vitro* (for example for diagnosis of disease) by T-cells from patients with cancer or if T-cells generated from these peptides could be used for treatment of disease as contemplated in the specification. Similarly to the above, Sherman et al, of record teach that self-tolerance may eliminate T cells that are capable of recognizing T-cell epitopes with high avidity , Smith, of record, teaches that antigen overload, due to antigen shedding by actively growing tumor, could block specifically either cytotoxic or proliferative responses of tumor specific T cells (again, even if precursor CTL exist in the system) (p. 847, last paragraph bridging p.848 and p.848). Smith further teaches that many tumors progressively lose MHC representation at the surface of the cell, and the loss of surface Class I MHC could severely limit the possibilities for cytotoxic T cells specific for a tumor specific antigen to find said tumor specific antigen in the necessary MHC context (p.484). Given the above, one would not know how to use the claimed peptides.

In addition, Boon, of record teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization and several lines of evidence, as set forth above, suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para 2). In addition, Boon teaches even if activated CTLs are significantly increased, the

therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells (p. 178, paragraph before last paragraph). Thus based on the teaching in the art and in the specification, one cannot predict that an adequate *in vivo* T cell response useful for induction of cytotoxic T lymphocytes that lyse cancer cells, as contemplated could be induced by the peptides that are claimed, in patients having tumor burden as contemplated. In addition, again as drawn to the unpredictability of *in vivo* T-cell response induction, , Kirkin et al, *Supra* review several melanoma-associated antigens, including NY-ESOl, and conclude that initiation of a strong immune response *in vivo* is an extremely rare event (p.674, first column, last paragraph). Kirkin et al teach that for some antigens, due to the existence of self-tolerance, only T cells with low affinity T-cell receptors are produced (abstract). Kirkin et a1 teach that although several peptides of melanoma associated antigens have been identified as recognized by CTL *in vitro,* and peptides from MAGE-A1 and MAGE-A3 have been tested for their ability to induce anti-melanoma immune response *in vivo,* only one of the peptides, peptide EVDPIGHLY of MAGE-A3, has limited anti-tumor activity, indicating their low immunogenicity p.666, second column, second paragraph, last 6 lines). Further, even this peptide EVDPIGHLY of MAGE-A3 produces a very low level of CTL response which is detectable only by a very sensitive method, as taught by Chaux et al, of record, abstract.

Finally, it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable. Although drawn to chemotherapeutic agents, the teachings of Gura (Science, 1997, 278:1041-1042) are relevant to the instant rejection. In particular, Gura teaches that researchers face the

problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs (which include immunotherapeutic protocols) have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for treatment of cancer (p. 1041, see first and second para). Given the above, because of the known unpredictability of the art, in the absence of experimental evidence in an appropriate animal model, with data commensurate in scope with the invention claimed, no one skilled in the art would believe it more likely than not that the claimed peptides would function as contemplated based only upon the *in vitro* studies exemplified.

Given the above, given the clear teaching of the art drawn to the unpredictability of the T-cell vaccine arts, given the lack of teaching drawn to whether or not SEQ ID NO:21 is even a naturally processed hTRT peptide, given the teachings of Gura, *Supra,* it is clear that the specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the claimed peptides would function as contemplated with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

Some of Applicant's arguments drawn to the prior rejection of claims 19, 21, 22, 24-41 under 35 USC 112, first paragraph are relevant to the instant rejection.

Applicant argues that the claims as currently constituted do not recite an intended use and therefore are enabled. The argument has been considered and has been found persuasive as drawn to SEQ ID NO:1 and SEQ ID NO:2, for the reasons set forth above, however for the reasons set forth above, the argument has not been found persuasive as it is drawn to SEQ ID NOS 21 and 22.

Applicant argues that SEQ ID NO:22 was shown to be suitable for inducing CTL that lyse hTRT human myeloma U255 cells using the methods of the instant application and points to Figure 4 and 5 of Hernandez et al (PNAS, 2002, 99:12275-12280.

The argument has been considered but has not been found persuasive for the reasons set forth above. Further, a review of Hernandez et al reveals that although PBMC of both normal and cancer patients were stimulated to produce CTL that lysed cells pulsed with SEQ ID Nos:21 and 22, and the reference suggests that the peptides are naturally processed in vivo in cancer cells, there is no teaching, as there is in the specification, that lysis of target cells by CTL from patient was inhibited by the cells pulsed with the peptides. Thus, it is not possible to determine whether of not SEQ ID NO:21 is naturally processed or whether it could be used for identifying CTL from patients with disease.

The arguments have been considered but have not been found persuasive and the claims are rejected for the reasons set forth above.

New Grounds of Objection

4. The disclosure is objected to because it is replete with embedded hyperlinks

and/or other forms of browser-executable code, for example at paragraphs 0063, 0082, 0086 of the published application. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP j 608.01 .It is noted that removal of the "http://" will disable the hyperlink and obviate this objection. Appropriate correction is required.

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.8821 (a)(1) and (a)(2), see for example pages 12, 14-16. However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because the specification if rife with sequences which are not identified by unique sequence identifiers. Examiner has made an effort to identify these informalities but applicant must carefully review the specification to identify and indicate where on the drawings numbered structures may be found. Appropriate correction is required.

Applicant is given the period of reply to this response within which to comply with the sequence rules. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821 (g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for response beyond the SIX MONTH statutory period.

6. Claims 43 and 44 are free of the art and allowable.

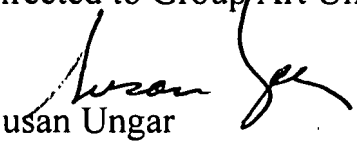
7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone

number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley, can be reached at 571-272-0898. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group/Art Unit 1642.



Susan Ungar
Primary Patent Examiner
June 19, 2007